ICDM2016-013: Non-Human Primate Models for Dyslipidemia and Dysglycemia Research

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INTRODUCTION

Obesity and diabetes are among the most serious public health issues of this century. They dynamically influence each other and often escalate patients' other health conditions. Obesity and diabetes associated comorbidities such as cardiovascular, renal, and other diseases have been studied for many decades. However, the precise underlying mechanisms of obesity and insulin-resistant diabetes and their reciprocal codependence have yet to be elucidated. It has been recognized that sustained greater energy intake than expenditure is the main cause of obesity which can potentially lead to insulin resistance and diabetes due to excessive fat accumulation. Various animal models have been induced and/or generated to understand the pathophysiology of obesity and diabetes and to test novel therapies. Compared with other animal species, non-human primates (NHPs) have greater similarities to human metabolism. Monkeys have been widely used in research for delineating molecular and cellular mechanisms of obesity and diabetes and also for testing new drugs and alternative novel therapies.

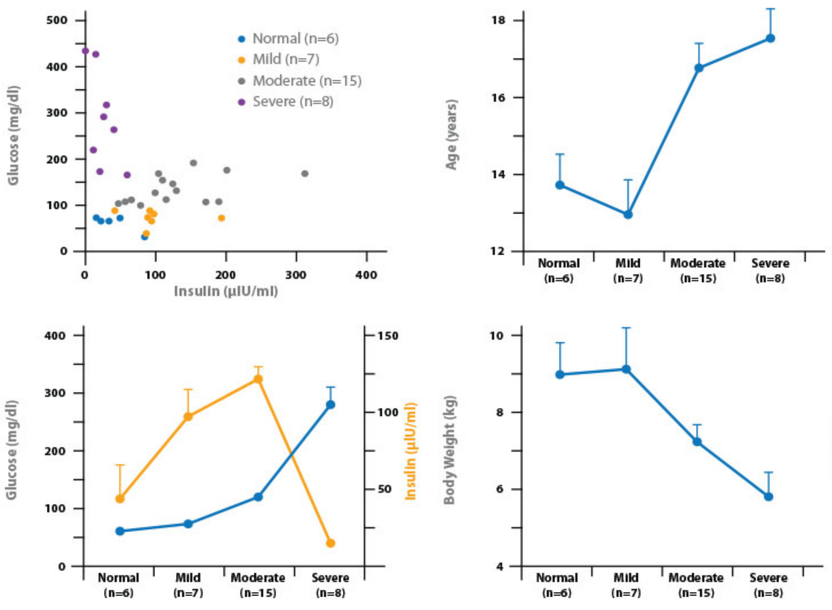
METHODS

Blood glucose and other chemical parameters were tested in a city hospital lab. Implanted telemetry devices were also used for continuous blood glucose monitoring. Body composition was analyzed with dual-energy x-ray absorptiometry (DXA) scan (GE Model: Lunar DPX-NT, Milwaukee, WI, USA). Each animal with overnight fasting was anesthetized initially with ketamine 10mg/kg i.m. and an additional 5mg/kg i.m. as needed. The animal was laid on its back and a DXA scan performed. Two X-ray beams with different energy levels were aimed at various organs and tissues. The scanned results were analyzed with the inbuilt DXA software.

RESULTS

Cynomolgus monkeys spontaneously develop diabetes and could be grouped based on their blood glucose/insulin levels (Fig. 1). The results from ivGTT, ITT, GGI, and clamp tests showed the impaired pancreatic function in diabetic monkeys (Fig. 2). Metformin reduced fasting glucose and HbA1c levels in diabetic monkeys (Fig. 3, left panel). Irbesartan treatment improved renal function in the diabetic nephropathy monkeys (Fig. 3, low panel). Natural obesity in NHPs could be a good model for obesity research (Fig. 4 and Table 1). High calorie diet (HCD) caused obvious dyslipidemia and some dysglycemia in NHPs (Fig. 5).

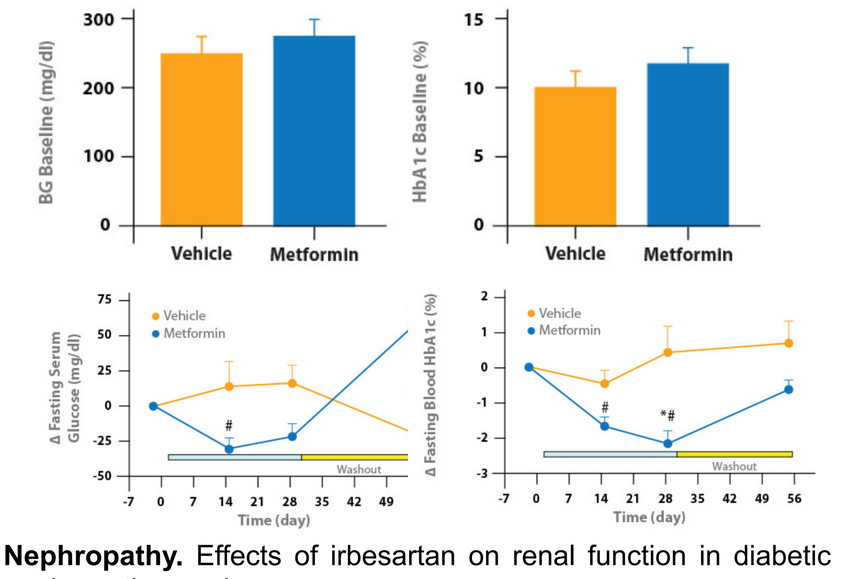
Fig 1. Grouping the Animals Based on their Fasting Glucose and Insulin Levels and the Progression of Spontaneously Developed Diabetes in NHPs



	Normal	Mild			Moderate			Severe
Glucose (mg/dl)	<80	80-100	or	<80	100-126	or	≥126	≥150
Insulin (μIU/ml)	<90			≥90			≥90	<50

Fig 3. Diabetic NHP Response to Treatment.

Metformin Treatment. Effects of metformin on fasting glucose and HbA1c levels in diabetic monkeys



Nephropathy. Effects of irbesartan on renal function in diabetic nephropathy monkeys

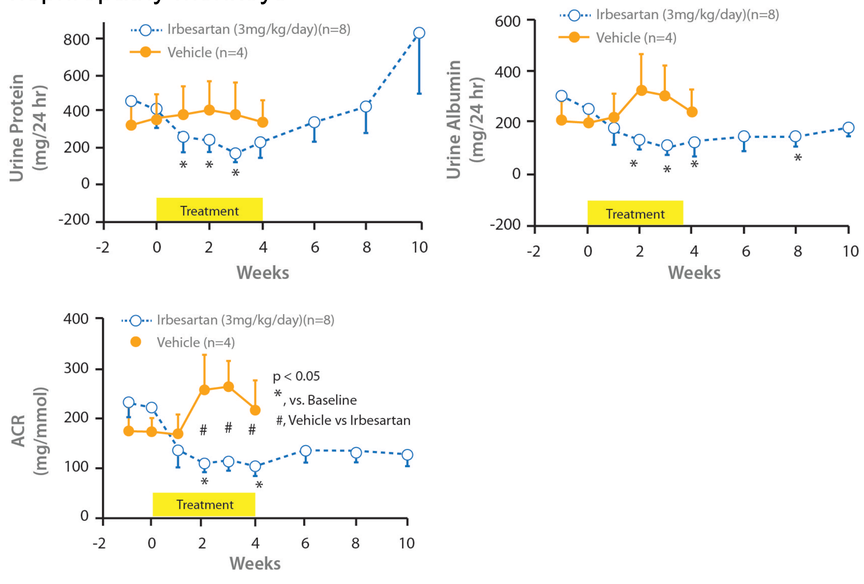


Fig 2. Impaired Pancreatic Function in Diabetic Monkeys

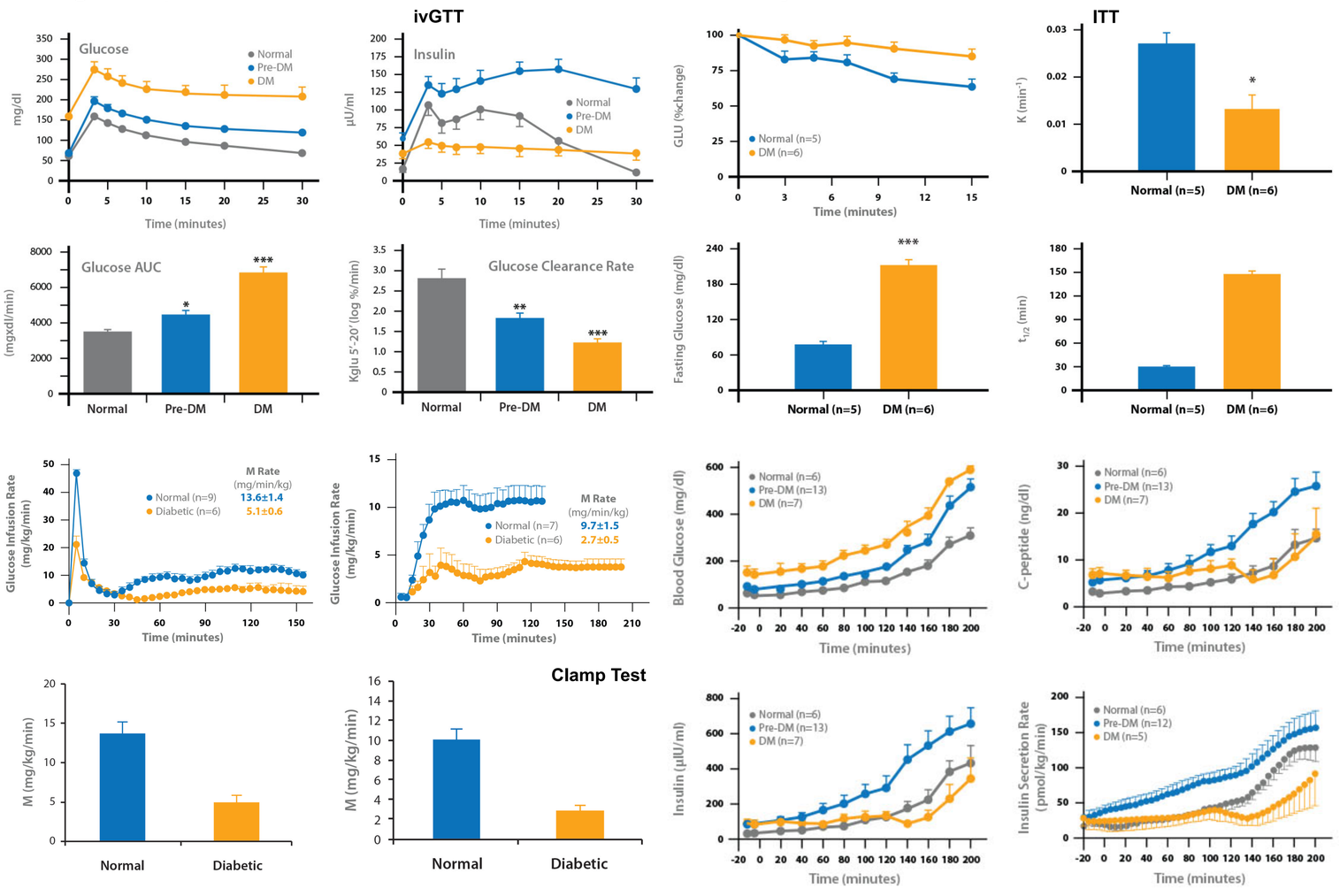


Table 1. General characteristics of the grouped monkeys fed with normal calorie diet

Parameter	Lean	Chubby	Obese	Morbidly Obese
	n=30 (M/F, 29/1)	n=26 (M/F, 25/1)	n=42 (M/F, 39/3)	n=5 (M/F, 5/0)
Age (yr)	11.5 ± 0.85	13.7 ± 0.67*	14.1 ± 0.35*	12.3 ± 2.13
Body weight (kg)	7.2 ± 0.39	9.3 ± 0.38*	10.6 ± 0.28*	13.6 ± 1.44*
Height (cm)	80.0 ± 1.08	82.6 ± 1.06	84.0 ± 0.70*	82.1 ± 1.19
Waist circumference (cm)	35.6 ± 1.36	44.0 ± 1.03*	50.3 ± 0.74*	62.5 ± 4.57*
BMI (kg/m^2)	11.1 ± 0.37	13.6 ± 0.37*	15.0 ± 0.27*	20.0 ± 1.65*
WHtR	0.44 ± 0.01	0.53 ± 0.01*	0.60 ± 0.01*	0.76 ± 0.05*
Total fat (%)	5.2 ± 0.31	15.1 ± 0.50*	26.6 ± 0.69*	43.9 ± 2.78*
Glucose (mg/dL)	144 ± 20.4	122 ± 18.5	112 ± 12.5	77 ± 8.4
Insulin (mIU/mL)	59 ± 13.2	254 ± 121.7	223 ± 67.6	107 ± 47.0
C-peptide (nmol/L)	1.35 ± 0.25	1.80 ± 0.21	1.84 ± 0.15	1.98 ± 0.93
TG (mg/dL)	146 ± 35.7	168 ± 46.1	143 ± 20.6	78 ± 11.1
TC (mg/dL)	141 ± 6.7	127 ± 7.5	119 ± 6.2*	136 ± 5.1
HDLc (mg/dL)	50 ± 4.2	48 ± 3.1	50 ± 2.4	65 ± 5.4
LDLc (mg/dL)	55 ± 3.9	42 ± 3.4*	46 ± 3.7	49 ± 6.0
Leptin (ng/mL)	11.7 ± 0.22	9.9 ± 0.86	9.8 ± 0.41*	10.6 ± 0.24*
CRP (mg/L)	2.7 ± 0.28	3.0 ± 0.79	1.7 ± 0.45	2.2 ± 0.40
WBC (10^9/L)	11.5 ± 1.21	11.3 ± 1.16	12.1 ± 0.69	13.2 ± 1.54

Note: M/F, male/female; BMI, body mass index = body weight/height^2; WHtR, waist-to-height ratio = waist circumference/height; *, $p < 0.05$, versus lean

Fig. 4. Grouping of the housed monkeys (*A*, n=103) and percentage distribution (*B*) based on their total fat percentages and criteria of obesity listed in Table 1.

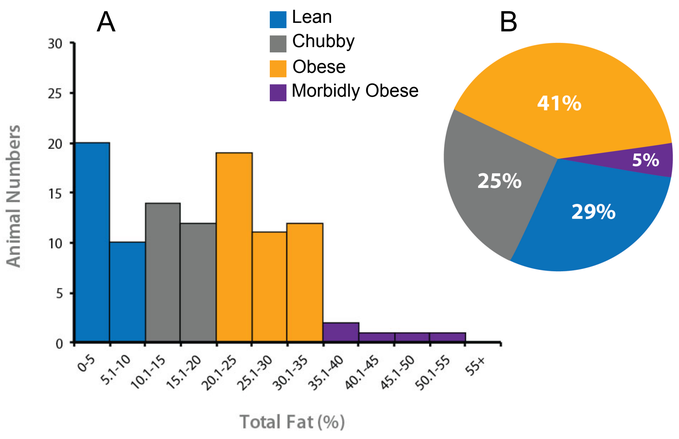
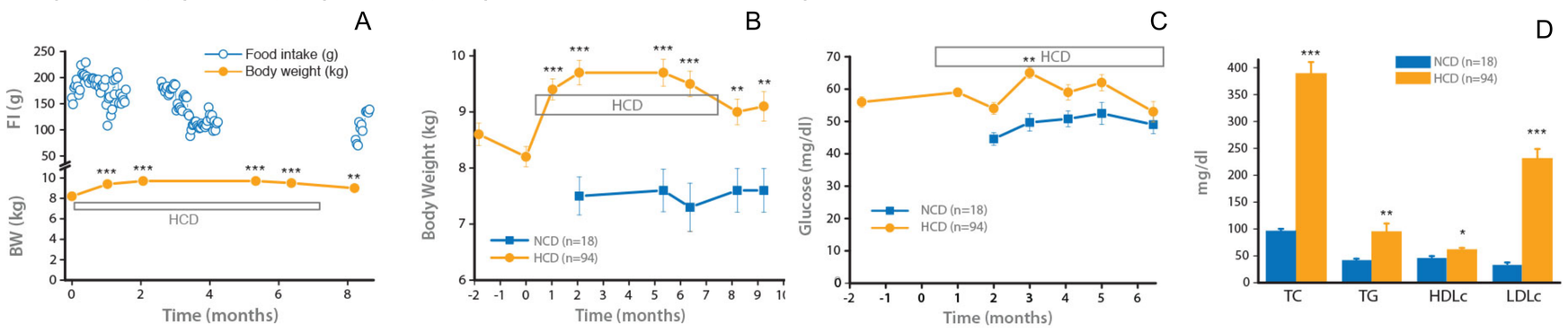


Fig. 5. Changes of food intake (FI) and body weight (BW) in normal NHPs (n=94) fed with a HCD (*A*). BW in normal NHPs fed with a norm calorie diet (NCD, n=18) or HCD (n=94) (*B*). Serum glucose in normal NHPs fed with a NCD or HCD (*C*). Serum lipids in NHPs fed either with a NCD or HCD (*D*).
*p<0.05; **p<0.01; ***p<0.001; vs pre-HCD or vs control in panel *D*.



SUMMARY

Various animal models have been induced and/or generated for research on understanding the pathophysiology of obesity and diabetes and to test novel therapies. Compared with other animal species, NHPs have greater similarities to the human metabolic system and mechanism. Monkeys have been widely used in research for delineating molecular and cellular mechanisms of obesity and diabetes and also for testing new drugs and other novel therapies. In recent years, we have conducted numerous studies in NHP models with either spontaneous or HFD-induced obesity (DIO) and diabetes. Dyslipidemia and/or dysglycemia data collected from a large number of diseased monkeys are reviewed and summarized in this presentation.